

Carcinoembryonic Antigen Production and Serum Levels in Esophageal Cancer

Masao TOMITA, Hiroyoshi AYABE, Katsunobu KAWAHARA
Shinsuke HARA, Yutaka TAGAWA and Hironobu TOCHIKA

*The First Department of Surgery, Nagasaki University School of
Medicine, Nagasaki, Japan.*

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ABSTRACT: In the forty-four patients with esophageal cancer, serum carcinoembryonic antigen (CEA) levels were evaluated between pre- and postoperative periods in comparison with patients between positive and negative tissue CEA staining.

Serum CEA levels were generally lower in patients with esophageal cancer and these showed less alteration in the postoperative period as compared with those in preoperative period. It is interest to emphasize that the survival following surgery in patients with negative tissue CEA staining in poor in this study.

This study indicated that low serum CEA levels were shown in spite of local production of CEA in cancer cells, reflecting a blockage to release CEA to blood stream.

It is believed that the variety of expression of cancer associated antigens is based on multiclonarity of cancer cells and/or alteration of expression of antigens with advances in tumor growth. However, it is dubious that CEA generated by carcinoma of the esophagus is indicative of aggressive behavior of the tumor and poor prognosis. Few reports are available in regard to expression of CEA antigen in patients with esophageal cancer. The pre-and postoperative CEA levels in patients with esophageal cancer remained unclear.

The purpose of this study is to clarify clinical values of CEA measurement in patients with esophageal cancers.

MATERIALS AND METHODS

During the time from November 1983 to June 1988, forty-four patients who underwent a resection of the esophagus for esophageal cancer at the First Department of Surgery, Nagasaki University Hospital were eligible for this study. The levels of serum CEA in the 44 patients were compared between pre-and postoperative periods, which were determined by a double antibody method¹⁾. Differentiation between normal and elevated CEA titers was based on 5.0ng/l as the upper normal concentration.

Tissue-CEA levels were also evaluated by staining method. Paraffin-embedded tissue were left at 38°C for 30min, removed paraffin using xylene and treated with 0.3% H₂O₂/MeOH for blockage of endogenous peroxidase and with swine for blockage of nonspecific finding by normal animal serum.

Preincubation was carried out for 15 minutes with normal goat serum diluted to 1:20, after which the cells were incubated in specific rabbit serum for one hour at room temperature. Antisera to CEA, purchased from Dakogatts were diluted to 1:400 and incubated with a secondary antibody, goat antirabbit IgG for 30 minutes and

then with PAP complex for another 30 minutes. Staining was done with 3,3-diaminobenzidine 4HCL for 10-15 minutes and counterstaining with 3 percent methyl green solution. Washing with PBS for 30 minutes was done between each step.

Positive staining of cells was regarded as over 20 percent of cells.

RESULTS

Table 1 showed an interrelation between positive tissue CEA and serum CEA. Most of esophageal cancers (67.9%) revealed positive tissue CEA staining. There was no close correlation between tissue CEA and serum CEA.

According to gross findings of esophageal cancer lesions as shown in Table 2, the degree of positive tissue CEA staining was dominant in ulcerative lesions and in view of histologic findings positive tissue CEA staining predominated in well and moderately differentiated carcinomas with not statistically significant difference. As for growing patterns, positive tissue CEA staining was dominant in the moderately or marked infiltration types as shown in Table 2. With respect to disease stages, high frequency of positive tissue CEA staining was seen in advanced cases such as a₂-a₃ and/or n₂-n₄ as shown in Table 3.

Table 4 showed a relationship between positive tissue CEA staining and histologic findings of vascular invasion (ly, v) and intraepithelial spread (ie). Histologic finding of vascular invasion closely correlated with positive tissue-CEA staining. The survival time were compared in patients between patients with positive and negative tissue CEA staining.

Fig. 1 showed a better survival curve in patients with positive tissue CEA staining. There was no survivors over 1.5 years in patients with negative tissue CEA staining as shown in Fig. 1.

The serum CEA levels in pre-and post-operative periods were compared between patients with positive and negative tissue CEA staining as shown in Fig. 2. Elevation of serum CEA was not remarkable in patients with esophageal cancer. In terms of the degree of tissue CEA staining, there was no characteristics of changes in serum CEA between pre-and

Table 1. Relationship between serum CEA levels and the degree of tissue CEA staining in esophageal cancer

	Serum CEA (-)	Serum CEA (+)
CEA STAIN -	7	0
CEA STAIN +	23	4
N. S.		

Table 2. Relationship of growth patterns and cell differentiation to tissue-CEA staining in esophageal cancer

	well.	mod.	poor.
CEA STAIN -	0	6	1
CEA STAIN +	14	20	3
N. S.			
	expan.	mod. inv.	mark. inv.
CEA STAIN -	1	5	1
CEA STAIN +	7	18	12
N. S.			

Table 3. Relationship between histologically cancer extension and the degree of tissue CEA staining in esophageal cancer

	a0	a1	a2	a3	
CEA STAIN −	1	3	2	2	
CEA STAIN +	13	6	11	8	
N. S.					
	n0	n1	n2	n3	n4
CEA STAIN −	2	0	0	1	2
CEA STAIN +	11	3	10	5	8
N. S.					

Table 4. Relationship between histologically cancer extension and tissue CEA staining

	ly (-)	ly (+)
CEA STAIN -	1	7
CEA STAIN +	14	22
N. S.		
	v (-)	v (+)
CEA STAIN -	1	7
CEA STAIN +	20	16
P<0.05		
	ie (-)	ie (+)
CEA STAIN -	4	3
CEA STAIN +	22	15
N. S.		

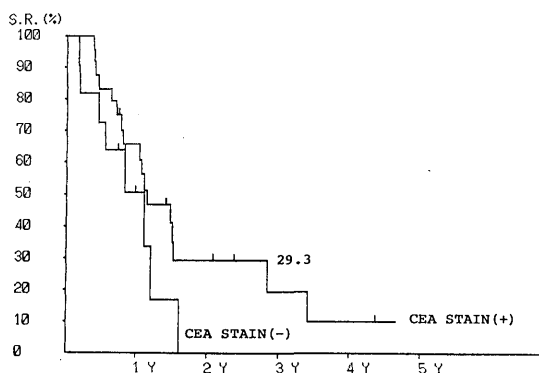


Fig. 1. The survival curve in comparison with patients between positive and negative CEA staining

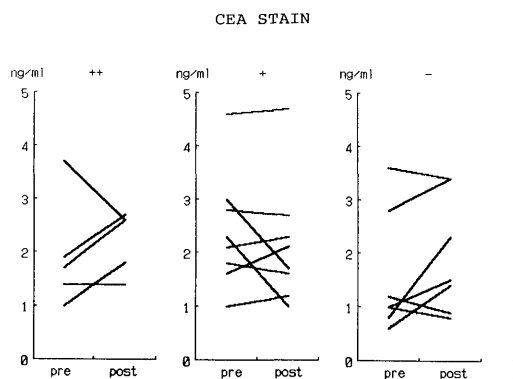


Fig. 2. Comparative observation of serum CEA levels between pre- and postoperative periods according to classification of the degree of tissue CEA staining

postoperative periods. However, in patients with negative tissue CEA staining there was less reduction of serum CEA levels by surgical removal of the tumors.

DISCUSSION

CEA is now widely utilized as markers of colorectal cancer. CEA is a glycoprotein antigen extracted from human colorectal cancer tissue and embryonal(2-6 months) intestinal tract by Gold *et al*²⁾ in 1965. It is well known that CEA is one of the most useful marker to detect carcinoma, in particular, the appearance of recurrence in the course of postoperative follow-up study. Some reporters clarified that CEA is predictive of a presence of well differentiated carcinoma in the colon, stomach,

breast and lung.

It is argued that positive tissue CEA staining correlated with aggressive behavior of the tumor. It is recognized that generation of cancer associated antigen is generally promoted in advanced cancers. Rosenthal³⁾ reported that CEA generation in culture cells is different from the parent cell line. It is controversial as to whether expression of cancer-associated antigens closely represents aggressive behavior of the tumor. Some⁴⁾ reported a close correlation between expression of CEA and prognosis, others⁵⁾ reported no close correlation.

Hamada⁶⁾ classified localization of tissue-CEA in colon cancers into the three types, Grade I (apical type), Grade II (cytoplasmic type), and Grade III (stromal type). He emphasized that serum-CEA levels increase in Grade III which includes the cases that are showing histologic finding of vascular invasion with poorly and moderate cell differentiations.

In general, marked elevation of serum CEA levels was not observed in patients with esophageal cancer.

Even after surgical removal of the tumor, serum CEA levels did not so much varied as to be predicted. It is a reflection that esophageal cancer lesions did not liberate CEA into the blood stream in spite of generation of CEA in cancerous lesions.

Interestingly enough, serum CEA levels in patients with negative tissue CEA staining were not influenced by surgical removal. It is accepted that serum CEA levels depend on a release of tissue CEA into the stroma⁸⁾.

In this study, it was evidenced that most of carcinomas of the esophagus generate CEA in cancerous lesions. On the contrary, serum CEA levels in esophageal cancer were lower than those in other cancers. It is well known that CEA generation in cancer cells means aggressive growth, poor prognosis, depressed immunoresponses and poor sensitivity to chemotherapy⁹⁾. This finding seems to be corresponded to clinical results of surgical treatment for esophageal cancers.

In contrast, Smith¹⁰⁾ reported that the prognosis of patients with breast cancer which showed strong tissue-CEA staining was favorable. Debate still continues regarding the clinical

significance of serum and tissue CEA levels in various cancers.

As far as esophageal cancer is concerned, this study indicated low serum CEA levels and high activity of CEA production in cancer cells. It is necessary to accumulate much study work on differentiation between serum and tissue CEA levels.

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